

GOODMAN and GILMAN's
The
Pharmacological
Basis of
Therapeutics

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In this textbook, reference to proprietary names of drugs is ordinarily made only in chapter sections dealing with preparations. Such names are given in SMALL-CAP TYPE, usually immediately following the official or nonproprietary titles. Proprietary names of drugs also appear in the Index.

GENERAL CONSIDERATIONS

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aneous mutation were the means by which microorganisms acquire resistance to antibiotics. Chemotherapy would, in theory, be a means of prevention. The frequency of mutation for resistance to one drug is about 10^{-6} to 10^{-8} per second drug 10^{-6} per independent mutation to resistance in a single cell is the frequency, 10^{-12} . The frequency of such mutations is statistically unlikely. In the method has received in the treatment of bacterial infections. A concomitant use of two or more agents strikingly different in their mode of drug resistance is not possible.

Uses of Combinations of Antibiotics

It is important that the use of combination agents. The most obvious toxicity from two or more antibiotics is the selection of microorganisms resistant to antibiotics that is necessary, and increased in addition, as noted in the antibacterial effect of bacteriostatic and bactericidal agents concurrently. The use of antibiotic antagonism is a method. Although antagonism by another has been demonstrated *in vitro*, well-known examples are the use of penicillin and streptomycin in the treatment of pneumococcal meningitis.

and Dowling reported that patients with pneumococcal meningitis were treated with penicillin and streptomycin. In those patients who received penicillin and chloramphenicol, 79% of the patients survived. This study was supported by the National Institutes of Health (1967), who reported that the mortality of meningitis of multiple organisms was significantly greater—100%—when treated with penicillin alone or with the combination of penicillin and chloramphenicol, and significantly greater—100%—when treated with penicillin alone than those treated with penicillin and streptomycin. The difference between antibiotics is not significant in most infections.

both agents must be active against the microorganism. The addition of a bacteriostatic drug frequently results in a bacteriostatic effect. In many infections, host defenses are adequate, this may still be enough to tip the balance in favor of the host. If host defenses are impaired, as in patients with neutropenia, or with special infections, such as endocarditis and meningitis, the bactericidal effect becomes more important. Certain studies in experimental animals and in the clinic support the use of penicillin and chloramphenicol are equally effective in preventing death. However, if the animals are irradiated and rendered neutropenic, the synergistic combination of gentamicin and chloramphenicol is much less effective than gentamicin alone in preventing death (Sande and Overton, 1974). In clinical trials in man, the more rapidly bactericidal combinations of antibiotics have been more effective than less rapidly bactericidal or purely bacteriostatic drugs in the therapy of negative infections in neutropenic patients.

PROPHYLAXIS OF INFECTION BY ANTIBIOTICS

A large percentage (from 30 to 50%) of antibiotics administered in the United States are given to prevent infection rather than to treat established disease. This practice accounts for some of the most flagrant abuses of these drugs.

Clinical studies have demonstrated that there are some situations in which chemoprophylaxis is highly effective and others in which it is totally without value and may in fact be deleterious. There are still numerous situations where the attempt to use antimicrobial compounds to prevent bacterial infection is controversial. In general, if a specific microorganism is known to be the cause of infection, then prophylaxis is usually successful. If the aim of prophylaxis is to prevent colonization or infection by any microorganisms present in the environment of a patient, then prophylaxis is usually unsuccessful.

Chemoprophylaxis has been employed for three purposes. (1) Prophylaxis may be utilized to protect healthy persons from acquisition of or invasion by specific microorganisms to which they are exposed. Successful examples of this practice include the following: the use of penicillin G to prevent infection by group-A streptococci; prevention of gonorrhea or syphilis after contact; the intermittent use of trimethoprim-sulfamethoxazole to prevent recurrent urinary tract infections usually caused by *E. coli*; the use of rifampin, minocycline, or sulfadiazine to prevent meningococcal disease. (2) Attempts are often made to prevent secondary bacterial infection in patients who are ill with other diseases. Examples of this form of prophylaxis have been efforts to prevent bacterial infection in patients with measles or in those in coma. Likewise, antibiotics are given to prevent infection in patients on respirators. This form of "total" chemoprophylaxis is usually unsuccessful. Resistant microorganisms, especially Enterobacteriaceae and fungi, emerge as pathogens and increase in frequency as prophylaxis is prolonged. Although certain centers have reported a decrease in the incidence of bacterial infections in neutropenic patients given trimethoprim-sulfamethoxazole, increased numbers of fungal infections were noted in some series. The normal microbial flora of the host represents an important defense in the prevention of colonization and infection with these pathogens (Sanders and Sanders, 1984). "Shotgun" chemoprophylaxis disrupts this barrier and may be self-defeating. Elaborate techniques involving sterile food, life islands, and nonabsorbable antibiotics have shown modest success in decreasing infections in neutropenic patients with hematological malignancies. (3) Chemoprophylaxis should be performed to prevent endocarditis in patients with valvular or other structural lesions of the heart who are undergoing dental, surgical, or other procedures that produce a high incidence of bacteremia. Endocarditis results from the bacterial colonization of the cardiac endothelium, particularly that of cardiac valves. The area of colonization is probably a deposit of fibrin and platelets on a damaged valve associated with areas of turbulent blood flow. The prophylactic use of antibiotics is therefore recommended in patients who have cardiac lesions, such as those produced by rheumatic or congenital heart disease that produce turbulence in blood flow. Any procedure

ture that injures a mucous membrane where there are large numbers of bacteria (such as in the oropharyngeal or gastrointestinal tract) will produce transient bacteremia. Streptococci from the mouth, enterococci from the gastrointestinal or genitourinary tract, and staphylococci from the skin have a propensity to produce endocarditis, and chemoprophylaxis directed against these microorganisms is recommended (Medical Letter, 1984). Therapy should not begin until immediately before the procedure, since prolonged administration of antibiotics can lead to colonization by resistant strains. Criteria have been established for the selection of specific drugs and patients who should receive chemoprophylaxis for various procedures (see Chapter 50).

Chemoprophylaxis to prevent wound infections after various surgical procedures has created considerable controversy. There are several well-controlled clinical studies that support the use of prophylactic antimicrobial agents in certain surgical procedures. The first such demonstration was by Bernard and Cole (1964), who showed the effectiveness of prophylactic antibiotics in patients undergoing operations involving the stomach, pancreas, and bowel. Wound infection results when a critical number of bacteria are present in the wound at the time of closure. Several factors determine the size of this critical inoculum, and these include the virulence of the bacteria, the presence of devitalized or poorly vascularized tissue, the presence of a foreign body, and the status of the host. Antimicrobial agents directed against the invading microorganisms may reduce the number of viable bacteria below the critical level and thus prevent infection.

Several factors are important to the effective and judicious use of antibiotics in this situation (Sandusky, 1979). First, antimicrobial activity must be present at the wound site at the time of its closure. This has led to the recommendation that the drug be given immediately preoperatively and, perhaps, intraoperatively. Second, the antibiotic must be active against the most likely contaminating microorganisms. This has prompted the wide use of first-generation cephalosporins in this form of chemo-

prophylaxis. Third, there is mounting evidence that the continued use of drugs after the surgical procedure is *unwarranted*. There are no data to suggest that the incidence of wound infections is lower if antimicrobial treatment is continued after the day of surgery (Rowlands *et al.*, 1982). Prolongation of use beyond 24 to 72 hours does, however, lead to the development of a more resistant flora and of wound infections caused by antibiotic-resistant strains. The risk of toxicity and unnecessary expense are, of course, additional disadvantages. In practice, however, this guideline is frequently broken. In a survey of the usage of antibiotics in Pennsylvania, where one third of all antimicrobial agents used were given for chemoprophylaxis, the median duration of such use was 7 days.

Chemoprophylaxis should be used only in selected operative procedures. A number of studies indicate that it can be justified in dirty and contaminated surgical procedure (e.g., resection of the colon), where the incidence of wound infections is high. These include less than 10% of all operations. In clean surgical procedures, which account for approximately 75% of the total, the expected incidence of wound infection is less than 5%, and antibiotics should not be used routinely. Exceptions are rational when the surgical procedure involves insertion of prosthetic implant. Although clear-cut data are not available to support the use of antibiotics during placement of prosthetic cardiac valves or artificial orthopedic devices, the complications of infection are so drastic that most authorities currently agree with this indication. Of course, the use of systemic antibiotics for chemoprophylaxis during surgical procedures does not reduce the need for clean and skilled surgical technique.

SUPERINFECTIONS CAUSED BY ANTIMICROBIAL AGENTS

The untoward reactions produced by anti-infective agents include toxic effects and hypersensitivity reactions. These are discussed for individual agents in the chapters that follow. Antibiotics also cause unique reactions that result from alteration in the microbial flora of the host.

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